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10/588,568	10/14/2009	Michael Tesar	047744-0125	8662

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/588,568	TESAR ET AL.
	Examiner	Art Unit
	ANNE GUSSOW	1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-89,91-96,98-105,107-113 and 115-141* is/are pending in the application.

4a) Of the above claim(s) *118-125 and 128-139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-89,91-96,98-105,107-113,115-117,126,127,140 and 141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.	6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/1/06, 9/5/08, 9/8/10, 4/8/11.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 85-89, 91-96, 98-105, 107-113, 115-117, 126, 127, 140, and 141, in the reply filed on April 8, 2011 is acknowledged. The traversal is on the ground(s) that the antibody of Logtenberg is an scFv molecule and does not have ADCC or CDC activity, thus the technical feature of the claims is special. This is not found persuasive because the Logtenberg reference was cited regarding the technical features of claim 138. The instant claim 138 does not require the antibody to have a specific activity, namely ADCC or CDC. The instant claim 138 is an independent claim and does not require any specific function of the antibody other than binding to the antigen CD38. As set forth in the restriction requirement mailed January 11, 2011 Logtenberg, et al. teach a method of producing a human scFv antibody fragment that binds to CD38 by contacting a synthetic library of human scFv antibody fragments expressed on phage particles with malignant plasma cells from patients with multiple myeloma. Thus, the method of producing the scFv fragment of Logtenberg reads on the instant claim 138.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 118-125 and 128-139 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 8, 2011.

3. Claims 85-89, 91-96, 98-105, 107-113, 115-117, 126, 127, 140, and 141 are under examination.

Priority

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Applicant's petition has been dismissed by the PCT office. Since the requested claim for priority does not affect the priority date received by the instant claims, the claims receive the date of February 6, 2004 for art rejection purposes.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on December 1, 2006, September 5, 2008, September 8, 2010, and April 8, 2011 have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states,

"the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

7. The disclosure is objected to because of the following informalities: the specification contains sequences which have not been identified by SEQ ID No. on the last line of page 46 and on page 47 of the specification as filed. It is not clear if these sequences have been included in the sequence listing. See 37 CFR §1.821-1.825.

Appropriate correction is required.

Claim Objections

8. Claims 140 and 141 objected to because of the following informalities: the claims depend from canceled claim 31. For the purpose of this office action is it assumed that claim 140 was intended to depend from claim 87. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 126 and 127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 126 and 127 recite a nucleic acid hybridizing under stringent conditions. It is unclear what is meant by stringent conditions. The specification discloses examples of stringent conditions (paragraphs 89-96, PG PUB numbering), but does not disclose the specific hybridization conditions which are stringent.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 85-89, 91, 92, and 117 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of the LP-1 or RPMI-8226 cell line is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the

invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different VH chains (about 50% homologous) can combine with the same VK chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different VK sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed cell lines LP-1 or RPMI-8226.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting cell lines and antibodies, this method will not necessarily reproduce cell lines which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could produce a LP-1 or RPMI-8226 cell line identical to those claimed. Undue experimentation would be required to screen all of the possible species to obtain the claimed cells.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed LP-1 or RPMI-8226 cell, a suitable deposit is required for patent purposes, evidence of public

availability of the claimed cell line or evidence of the reproducibility without undue experimentation of the claimed cell line, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the cell lines has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of the cell line is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

> (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:
> (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:
> (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the

furnishing of a sample of the deposited biological material, whichever is longest; and
(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

13. Claims 85-89, 91-96, 98-105, 107-113, 115-117, 126, 127, 140, and 141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a functional fragment of an antibody. The claims are also drawn to an antibody that competes for binding with an antibody that binds to an epitope of CD38. The claims are also drawn to an antibody which has 60% sequence identity within the CDR regions to a heavy chain and a light chain variable region (claims 140 and 141).

The specification discloses fragments of antibodies which bind to antigen. The specification does not provide sufficient written description as to the structural features of the claimed genus of antibody fragments. The specification does not disclose which fragments of antibodies would maintain function. The specification does not disclose antibodies with any mutations within the CDR regions of the heavy chain or the light chain variable region.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus

after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for identifying an antibody fragment encompassed by the claimed specificity. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required.
Skolnick, et al. (Trends in Biotechnology, 2000. Vol. 18, pages 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based on sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a

similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to function of the structurally related protein (see in particular "Abstract" and Box 2).

Additionally, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745, as cited on the IDS filed September 8, 2010) who analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs

coincide with residues as important in defining canonical backbone conformations (see page 735, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by Casset, et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205, as cited on the IDS filed September 8, 2010) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos, et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428, as cited on the IDS filed September 8, 2010) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Wu, et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162, as cited on the IDS filed September 8, 2010) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left

column) but certain residues have been identified as important for maintaining conformation.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only antigen binding fragments, the heavy chain of SEQ ID No. 6, and the light chain of SEQ ID No. 14, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

14. Claims 126 and 127 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to variable heavy and light chain sequences encoded by a specific nucleotide sequence or a nucleic acid sequence that hybridizes under stringent conditions to a nucleotide sequence complementary to a nucleic acid sequence.

The specification discloses antibodies encoded by specific amino acid sequences encoded by specific nucleic acid sequences.

The specification does not provide sufficient written description as to the structural features of the claimed genus of nucleic acids and encoded polypeptides and the correlation between the chemical structure and function of the genus of nucleic acids, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded. The nucleic acids that hybridize to the complement of SEQ ID No. 1, for example (although the rejection applies to each of the SEQ ID Nos.) would comprise a large range of diversity because molecules which hybridize would not specifically bind to each and every residue of a sequence. Thus, one of ordinary skill in the art would not know the structure of the hybridizing nucleic acids that would be associated with the binding activity. Further, the nucleic acid that hybridizes would not encode a heavy chain or a light chain variable region of an antibody.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A

patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences are essential, which sequences are non-essential and what particular sequence lengths identify essential sequences for identifying a nucleic acid encompassed by the claimed specificity. For example, there is insufficient guidance based on the reliance of disclosure of SEQ ID Nos. 1-4 or 9-12 to direct a person of skill in the art to select or to predict particular sequences as essential for identifying nucleic acids encompassed by the claimed specificities. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required. Skolnick et al (Trends in Biotechnology, 2000. Vol. 18, pages 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based on sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to

function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to function of the structurally related protein (see in particular "Abstract" and Box 2).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology, 1990. Vol 111, pages 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar, et al. Molecular and Cellular Biology, 1988. Vol 8, pages 1247-1252).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance on the binding of the polypeptide encoded by SEQ ID Nos. 1-4 or 9-12 disclosed in the specification as-filed does not appear to provide sufficient written description for the genus of nucleic acids encompassed by the claimed specificities in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single

species encompassed by the highly variant genus nor is there disclosure of the common attributes or features (i.e., structural domains) that are essential for activity or those which are non-essential. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids comprising SEQ ID Nos. 1-4 and 9-12, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

15. Claims 126, 127, 140, and 141 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody encoded by the nucleic acid sequence of SEQ ID Nos. 1-4 and 9-12 or and antibody comprising SEQ ID Nos. 6 or 14, does not reasonably provide enablement for a nucleic acid that hybridizes to the complementary strand of SEQ ID Nos. 1-4 or 9-12 encoding an antibody, or an antibody that comprises 60% identity in the CDR regions of SEQ ID Nos. 6 or 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to an antibody encoded by a nucleotide sequence which hybridizes under high stringency conditions to the complementary strand of SEQ ID Nos. 1-4 or 9-12. The claims are also broadly drawn to an antibody or functional fragment thereof that comprises an amino acid sequence having 60% identity in the CDR regions with SEQ ID No. 6 or 14.

The specification discloses antibodies that bind to CD38 encoded by the nucleotide sequences of SEQ ID Nos. 1-4 and 9-12. The specification discloses the heavy chain amino acid sequence of SEQ ID No. 6 and the light chain amino acid sequence of SEQ ID No. 14. The specification does not disclose nucleotide sequences that hybridize to the complement of SEQ ID Nos. 1-4 or 9-12 and encode an antibody. The specification does not disclose any amino acid mutations in the antibody sequences.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs

are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol 79 page 1979). Rudikoff, et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, 732-745, as cited on the IDS filed September 8, 2010) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). De Pascalis, et al. (Journal of Immunology, 2002. Vol. 169, 3076-3084, as cited on the IDS filed September 8, 2010) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the

structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset, et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205, as cited on the IDS filed September 8, 2010) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset, et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos, et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428, as cited on the IDS filed September 8, 2010) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm, et al. (Molecular Immunology, 2007. Vol. 44, pages 1075-1084, as cited on the IDS filed September 8, 2010) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen,

et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881, as cited on the IDS filed September 8, 2010) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu, et al. (Journal Molecular Biology, 1999. Vol.294, pages 151-162, as cited on the IDS filed September 8, 2010) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce a functional antibody that binds to CD38 encoded by a nucleic acid that hybridizes to a complement of a nucleic acid that encodes an antibody or an antibody that binds to CD38 comprising 60% identity to the CDR regions. The specification does not teach how to make an antibody that would bind CD38 and comprise less than 100% identity to the disclosed CDR regions.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to make the claimed antibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the claimed antibody and absent working examples providing evidence which is reasonably predictive that the claimed antibodies are effective binding molecules, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 100, 101, 107, 108, and 117 are rejected under 35 U.S.C. 102(a, e) as being anticipated by Logtenberg, et al. (US PG PUB 2003/0211553, published November 13, 2003, priority to July 19, 2000, as cited on the IDS filed September 5, 2008).

The claims recite an isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that competes for binding with an antibody which specifically binds to an epitope of CD38, wherein the epitope comprises an amino acid residue between 1 to 215 of CD38 (SEQ ID NO: 22), wherein the epitope comprises an amino acid residue found within amino acids 44-66, 82-94, 142-154, 148-164, 158-170, or 192-206 ofCD38 (SEQ ID NO: 22), which is an IgG, which is an IgG1. A pharmaceutical composition comprising an antibody or functional fragment thereof according to claim 85 and a pharmaceutically acceptable carrier or excipient therefor.

Logtenberg, et al. teach a human UM16 antibody that binds to CD38 that competes for binding with the OKT10 antibody (see figure 8). Logtenberg, et al. teach the antibody in a pharmaceutical composition for the treatment of disease (paragraph 7). Since the claims are drawn to an antibody that competes for binding with an antibody that binds to CD38 and Logtenberg, et al. teach a UM16 antibody that competes for binding with the OKT10 antibody, all the limitations of the claims have been met.

Conclusion

18. No claims are allowed..

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
July 14, 2011

/Anne M. Gussow/
Primary Examiner, Art Unit 1643